REMARKS

Claims 1, 4-7, 11 and 13 are pending in this application. Claims 2-3, 8-10 and 12 were canceled in this amendment. Claims 14 and 15 were withdrawn without prejudice pursuant to the restriction requirement.

Claim Rejections -- 35 USC § 112

Claims 1-10 were rejected under 35 U.S.C. 112, first paragraph. Applicants have changed the range of the molar ratio in claim 1 from 1:0 to 1:1.0 to 1:0.01 to 1.0. This amendment is supported by Table 1 on page 18 of the specification, which specifically cites this molar ratio. Applicants respectfully submit that this rejection has been overcome.

Claim Rejections -- 35 USC § Sec. 103(a)

Claims 1-13 were rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/096396 in view of Yamaguchi et al. (March 2002) and the Merck Index. U.S. Patent Application Publication 20004/0185113 is cited by the Examiner as an English language translation of WO 02/096396.

WO02/096369 (US2004/0185113 A1) discloses drug-encapsulating inorganic microparticles and a production method thereof. The microparticles disclosed in WO02/096369 comprise a biologically active substance coated with calcium carbonate (see claims 1 and 6 of US2004/0185113 A1). The production method of the microparticles taught by this reference comprises the steps of 1) preparing an aqueous solution of a calcium salt; 2) adding a biologically active substance into the aqueous solution; and 3) adding a carbonate into the mixed solution to encapsulating the biologically active substance with calcium carbonate (see claim 12).

WO02/096369 describes that this method can produce microparticles having an average particle size of 10 nm to 100 μm (see paragraph [0024]). However, WO02/096369 fails to disclose any example of an actual product of microparticles having

an average particle size of 5 to 106.4 nm. WO02/096369 describes that a surfactant may be added into the reaction solution to prevent the aggregation of the microparticles (see paragraph [0023]). However, WO02/096369 does not specify the type of surfactant, nor which step in the method when a surfactant is added.

Yamaguchi et al. (The Journal of Pharmaceutical Science and Technology, March 2002, 1-2, Vol.62, Supplement) discloses retinoic acid nanoparticles and a production method thereof. The nanoparticles disclosed in Yamaguchi et al. comprise spherical micelles of retinoic acid coated with calcium carbonate (see "Objective"). The production method of the nanoparticles comprises the steps of 1) forming micelles of retinoic acid in aqueous solution; and 2) adding $CaCl_2$ and $NaCO_3$ into the aqueous solution (see "Experimental methods"). The retinoic acid nanoparticles have a diameter of about 125-164 nm (see "Results and Discussion").

The Merck Index (The Merck Index, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ, page 1404, entry no. 8333 (retinoic acid), 1996) discloses general information about retinoic acid.

The claimed invention in amended claim 1 differs from the inventions of WO02/096369 and Yamaguchi et al. in that i) a nonionic surfactant is used to form a mixed micelle of retinoic acid and nonionic surfactant; and ii) retinoic acid is dispersed in aqueous solution containing alkali.

Regarding the above-mentioned technical feature i), as described in the specification of the present application, upon coating micelles of retinoic acid with an inorganic salt (calcium carbonate), there is a problem of aggregation of micelles of retinoic acid. To avoid this problem, it is proposed in the present invention that micelles of retinoic acid are produced as mixed micelles of retinoic acid and nonionic surfactant. In this regard, the specification of the present application describes as follows:

> "*The surface of the micelle is negatively charged and readily adsorbs (binds to) divalent metal ion...replacing sodium ion. Since the divalent metal ion is more tightly adsorbed (bound) to the micelles than is the sodium ion, the micelles having the divalent metal ions adsorbed on them have more stable surface charge, so that*

they become insoluble in water and precipitate. The precipitated particles aggregate into large clusters...To prevent aggregation of the charged particles, a nonionic surfactant...is added along with retinoic acid." (page 11 lines 1-11 of the specification)

In this regard, it is important to use a nonionic surfactant rather than an ionic surfactant. For example, if the micelles are prepared as mixed micelles of retinoic acid and cationic surfactant, the cationic surfactant reacts with carboxylic groups of retinoic acid, and thus the micelles become insoluble in water and precipitate. Therefore, it is necessary to use a nonionic surfactant rather than an ionic surfactant in order to prepare the claimed retinoic acid nanoparticles having an average particles size of 5 nm to 106.4 nm.

In addition, it is important to form mixed micelles of retinoic acid and nonionic surfactant by adding a nonionic surfactant before adding calcium halide or acetate (Ca^{2+}). Once micelles of retinoic acid are coated with Ca^{2+}, the micelles become insoluble in water and aggregate into large clusters (page 11 lines 3-8 of the specification). These large clusters cannot disintegrate into individual micelles by the addition of a nonionic surfactant. Therefore, it is necessary to add a nonionic surfactant before adding calcium halide or acetate (Ca^{2+}) in order to prepare the claimed retinoic acid nanoparticles having an average particles size of 5 nm to 106.4 nm.

Regarding the above-mentioned technical feature ii), it is necessary to disperse retinoic acid in an aqueous solution in order to form micelles of retinoic acid. The present inventors found that it is necessary to use an aqueous solution comprising alkali in order to disperse retinoic acid in an aqueous solution (page 10 line 29 to page 11 line 1 of the specification).

On the other hand, although WO02/096369 discloses the use of a surfactant to prevent the aggregation of microparticles, WO02/096369 fails to disclose the use of nonionic surfactant as the surfactant and the time at which a surfactant is added.

Yamaguchi et al. discloses neither the above problem associated with the aggregation of micelles nor the use of a surfactant for avoiding this problem.

In addition, WO02/096369 and Yamaguchi et al. do not describe that a biologically active substance (retinoic acid) is dissolved in an aqueous alkali solution.

As mentioned above, it is possible to produce retinoic acid nanoparticles having an average particles size of 5 to 106.4 nm by combining the above-mentioned technical features i) and ii). However, the features 1) and 2) are not described in WO02/096369 and Yamaguchi et al. Therefore, the skilled person would not be able to produce retinoic acid nanoparticles having an average particles size of 5 to 106.4 nm by using an aqueous alkali solution and nonionic surfactant based on the disclosures of WO02/096369, Yamaguchi et al. and The Merck Index. In fact, nanoparticles having an average particles size of 5 to 106.4 nm cannot be produced in WO02/096369 and Yamaguchi et al.

Therefore, Applicant respectfully submits that the claimed invention in amended claim 1 is not obvious over the cited WO02/096369, Yamaguchi et al. and The Merck Index, either taken alone or in combination.

The claimed inventions in amended claims 11 and 13 differ from the inventions of WO02/096369 and Yamaguchi et al. in that i) nanoparticles comprise a nonionic surfactant; and ii) nanoparticles have an average particle size of 5 to 106.4 nm. As mentioned above, the skilled person would not be able to produce retinoic acid nanoparticles comprising nonionic surfactant and having an average particle size of 5 to 106.4 nm based on the disclosures of WO02/096369, Yamaguchi et al. and The Merck Index. Therefore, Applicant submits that the claimed inventions in amended claims 11 and 13 are not obvious over the cited WO02/096369, Yamaguchi et al. and The Merck Index, either taken alone or in combination.

Claim Rejections – Provisional Nonstatutory Obvious-Type Double Patenting

Claims 1-13 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-21 and 24-28 of copending Application No. 10/595,413. Applicants are hereby submitting a terminal disclaimer with regard to the copending application, which they submit overcomes this rejection.

CONCLUSION

If the Examiner has any questions, he is respectfully requested to contact the undersigned. The Commissioner is hereby authorized to charge any additional fees, or to credit any overpayment, to Deposit Account No. 50-3195.

Respectfully submitted,

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/Manette Dennis/

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Appendix:
Terminal Disclaimer